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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,458	03/17/2004	Patrick Fogarty	TOSK-006CON	5491

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	PAPER NUMBER
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,458	FOGARTY, PATRICK	
	Examiner	Art Unit	
	Chris E. Simmons	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *12-16 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :06/15/2004 08/24/2005 09/29/2005 01/09/2007.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-11 and 17-27) in the reply filed on 02/16/2007 is acknowledged. The traversal is on the grounds of lack of search burden on the Examiner. This is not found persuasive because there would be a serious burden on the examiner if restriction is not required because the distinct inventions have acquired a separate status in the art in view of their different classification. Each invention may not be anticipated by others because each invention is patentably distinct to each other as evidenced by numerous patents (see US626845, US5854227, US6133317, US6207152 B1, or US4975434). For example, methods of treating cancer (a cellular proliferative disease) with different products are classified under 514/274, 514/574, 514/79, 424/145.1, or 424/130.1. Furthermore, even if there were unity of classification, the search of the entire genus in the non-patent literature (a significant part of a thorough examination) would be burdensome. Thus, restriction for examination purposes as indicated is proper. See MPEP § 808.02.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-16 and 28-30 are withdrawn.

Priority

2. This application claims priority to Application No. PCT/US02/29669, International Filing Date: 09/20/2002, pursuant to 35 U.S.C. Section 119(e), claims priority to the

filing date of US provisional application 60/324566, Filing date of 09/24/2001. Priority claim is acknowledged and granted.

Specification

3. The disclosure is objected to because of the following informalities: the structure of TK-5145 on page 5 needs to be corrected due to overlapping nodes. The double bonded oxygen in the ester group overlaps the methyl group attached to the phenyl ring.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering to a subject in need thereof, cisplatin in conjunction with an amount of TK-211 effective for reducing the toxicity of cisplatin, does not reasonably provide enablement for a method of administering a "cisplatin active agent" in conjunction with a "cisplatin toxicity-reducing agent. Furthermore, the phrases "cisplatin active agent" and "cisplatin toxicity-reducing agent" are too broad and needs to be defined. One of ordinary skill in the art would not be enabled to practice the claimed invention. These phrases read on any agent and

would require undue experimentation to determine what a "cisplatin active agent" or "cisplatin toxicity-reducing agent" is.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant claims a method of administering to a subject in need thereof, said method comprising: administering to said host said effective amount of a cisplatin active agent in conjunction with an amount of a cisplatin toxicity reducing agent effective to reduce toxicity of said cisplatin active agent.

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Unpredictability of the art. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant "agents". Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Scope of the claims. The claims are broad and read on hundreds of compounds. The phrase "cisplatin toxicity-reducing agent" reads on any agent. The phrase "cisplatin-active agent" reads on any agent. These terms are too broad to claim.

Relative skill of those in the art. The relative skill of those in the art of pharmaceuticals is high.

The breadth of the claims. The breadth of the claims is further exacerbated by the instantly claimed compounds where full scope of claimed compounds are not enabling. The specification only discloses the reduction of cisplatin toxicity by administering cisplatin in combination with TK-211.

The amount of direction or guidance presented. The specification discloses the results of study involving cisplatin in combination with an amount of TK-211 effective to reduce the toxicity of cisplatin. Applicant's limited guidance does not enable the public to use all the claimed combinations in decreasing the cisplatin active agent toxicity. For instance, Applicant merely states how to reduce the toxicity of cisplatin by administering cisplatin in combination with TK-211. There is no guidance for how to make or utilize all the claimed compositions in to reduce cisplatin toxicity+.

The presence or absence of working examples. As stated above, the specification only provides the usefulness of reducing the toxicity of cisplatin by administering cisplatin in combination with TK-211 for ovarian cancer treatment. The specification fails to provide adequate representation regarding other compounds in combination.

The quantity of experimentation necessary. Since the administering a cisplatin active agent using a combination of cisplatin active agent and a cisplatin reducing agent cannot be predicted from a priori but must be determined from case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Given the analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have to conduct undue and excess experimentation in order to practice the claimed invention.

6. Claims 17-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling for** a method for the **amelioration** of undesirable **symptoms** due to toxicity of **cisplatin** given to a **patient** suffering from cancers **in which cisplatin is effective** by administering **cisplatin and TK-211**, does not reasonably provide enablement for the treatment (as broadly defined in specification) or amelioration of symptoms afflicting a host suffering from any cellular proliferative disease by administering a “cisplatin active agent” in conjunction with a “cisplatin

toxicity-reducing agent". Furthermore, the phrases "cisplatin active agent" and "cisplatin toxicity-reducing agent" are too broad and needs to be defined. One of ordinary skill in the art would not be enabled to practice the claimed invention. These phrases read on any agent and would require undue experimentation to determine what a "cisplatin active agent" or "cisplatin toxicity-reducing agent" is.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant claims a method of treating a host suffering from a cellular proliferative disease condition, said method comprising: administering to said host said effective amount of a cisplatin active agent in conjunction with an amount of a cisplatin toxicity reducing agent effective to reduce toxicity of said cisplatin active agent so that said host is treated for said cellular proliferative disease condition. However, Applicant broadly defines "treatment" in paragraph 44:

> [0044] "By treatment is meant that at least an amelioration of the symptoms associated with the condition afflicting the host is achieved, where amelioration is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g. symptom, associated with the condition being treated. As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, e.g., prevented from happening, or stopped, e.g. terminated, such that the host no longer suffers from the condition, or at least the symptoms that characterize the condition."

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term

"undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Unpredictability of the art. The art with regard to treating hosts suffering from a cellular proliferative disease is unpredictable. Essentially, a skilled artisan would need to practice trial and error experimentation of administering the claimed composition to subjects with randomly selected cellular proliferative diseases associated with cisplatin.

Scope of the claims. The claims are broad and read on hundreds of diseases with different pathological pathways. The phrase "cisplatin toxicity-reducing agent" reads on any agent. The phrase "cisplatin-active agent" reads on any agent. The phrase "cellular proliferative disease" reads on all cancers and hyperplasias. These terms are too broad to claim.

State of the art. The art in the field of cancer treatment has not developed to the level in which pharmaceuticals can prevent, eliminate or terminate the cause of any cancer or toxic effects caused by the cancer treating drug.

Relative skill of those in the art. The relative skill of those in the art of pharmaceuticals is high.

The breadth of the claims. The instant claims embrace the therapeutic treatment of all cellular proliferative disease. The instant claims cover "cellular proliferative disorders" that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The breadth of the claims is further exacerbated

by the instantly claimed compounds where full scope of claimed compounds are not enabling. The specification only discloses the reduction of cisplatin toxicity by administering cisplatin in combination with TK-211.

The amount of direction or guidance presented. The specification discloses the results of study involving cisplatin in combination with TK-211 in ovarian cancer cells. Applicant's limited guidance does not enable the public to use all the claimed combinations and further administer the claimed invention for the treatment of all the possible cellular proliferative diseases. For instance, Applicant merely states how to reduce the toxicity of cisplatin by administering cisplatin in combination with TK-211. There is no guidance for how to make or utilize all the claimed compositions in the treatment for all cellular proliferative diseases.

The presence or absence of working examples. As stated above, the specification only provides the usefulness of reducing the toxicity of cisplatin by administering cisplatin in combination with TK-211 for ovarian cancer treatment. The specification fails to provide adequate representation regarding treating all cellular proliferative diseases.

The quantity of experimentation necessary. Since the treatment of all cellular proliferative diseases using a combination of cisplatin and TK-211 cannot be predicted from a priori but must be determined from case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Given the analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have to conduct undue and excess experimentation in order to practice the claimed invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-8, 10-11, 17-24 and 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "cisplatin active agent" in claims 1-8 is a relative phrase, which renders the claim indefinite. The phrase "cisplatin active agent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, “cisplatin active agent” can be interpreted as “cisplatin as an active agent” or a “cisplatin activating agent” or “active cisplatin isomer or derivative thereof”. Clarification is required.

9. Claim 1 recites the limitation "said host" in the 3rd line. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 17 recites the limitation "said effective amount" in the 3rd line. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 and 17-26 are rejected under 35 U.S.C. 102(b) as being anticipated by WO/1998/014182 (herein referred to as "Campbell").

The instant claims read on a method of administering to a host suffering from a cellular proliferative disease condition, comprising administering an effective amount of cisplatin active agent and cisplatin toxicity-reducing agent. Said reducing agent can be administered at the same time, before or after.

Campbell teaches the present invention relates to the use of protective agents in cancer chemotherapy in human and animal subjects. Protective agents are compounds that prevent, reduce, or otherwise ameliorate the toxic side effects of anti-cancer chemotherapeutic compounds in normal body cells while substantially preserving the anti-tumor properties of these compounds in vivo when administered prior to, concomitantly with, or subsequently to administration of such chemotherapeutic compounds. More specifically, the invention relates to the use of D-methionine

(molecular weight of 149.21 and, therefore, reads on "small organic compound" as defined in paragraph 26 of instant application) and structurally related compounds as protective agents having oto- protective, weight loss-protective, gastrointestinal-protective, neuro-protective, alopecia-protective, and survival-enhancing effects in conjunction with chemotherapy employing platinum-containing antineoplastic agents, such as cisplatin. (p. 1 *Field of Invention*; 1st paragraph under *Summary of Invention;* Claims.)

Campbell teaches each compound can be formulated individually and administered separately or at the same time. Alternatively, both can be contained together in a single dosage formulation. (Last paragraph under *Administration of Methionine Protective Agents; page 32)*

As for claims 8 and 24, Campbell teaches that the effective amount of methionine protective (D-methionine) agent can be in the range of from about 0.1 mg/kg body weight to about 500 mg/kg body weight (paragraph 88 under *Dosages*). Campbell also teaches that cisplatin can be administered in dosages as low as 10 mg/m^2. The Toxicologist's Pocket Handbook published in 2000 teaches on page 16 that to express a mg/kg as the equivalent mg/m^2 dose, multiply by the dose by 37 mg/m^2 for human adults. If Campbell's teaching of the range from about 0.1 mg/kg to about 500 mg/kg of D-methionine is converted to its equivalent mg/m^2 using the Toxicologist's Pocket Handbook published in 2000, the mg/m^2 equivalence for D-methionine would be:

Low Range Dose	X	37 mg/m^2	High Range Dose	X	37 mg/m2
0.1 mg/kg	X	37 mg/m^2	500 mg/kg	X	37 mg/m^2
3.7 mg/m^2			18500 mg/m^2		

Consequently, the range of 3.7 mg/m^2 to 18500 mg/m^2 of D-methionine in Campbell teaches an amount of methionine (3.7 mg/m2) that is not more than the amount of cisplatin (10 mg/m^2) and, therefore, anticipates the claimed invention of the amount of cisplatin toxicity-reducing agent being not more than about the amount of cisplatin active agent.

Allowable Subject Matter

12. Please take note that claim 1 is drawn to a method of administering to a subject in need thereof an effective amount of a cisplatin active agent and a cisplatin toxicity-reducing agent comprising administering said effective amount of a cisplatin active agent and a cisplatin toxicity-reducing agent effective to reduce toxicity of said cisplatin active agent. However, claim fails to explain what is meant by "an effective amount of a cisplatin active agent".

Claim 1 **would be allowable if** it was rewritten or amended to overcome the rejections under 35 U.S.C. 112, 1st and 2nd paragraphs, set forth in this Office action.

If Applicant makes these amendments, the following claim drafted by the Examiner would be considered to distinguish patentably over the art of record in this application and is presented to applicant for consideration:

Claim 1. A method of administering to a subject in need thereof an amount of cisplatin, said method comprising:

administering to said subject cisplatin in conjunction with an amount of TK-211 effective to reduce toxicity of said cisplatin.

If claims 2-8 were amended according to MPEP guidelines to read consistent with the limitations of Examiner-recommended claim 1, then these claims would be allowable. Claims 9-11 would need to be canceled.

13. Please take note that claim 17, in its current form, is drawn to *a method of treating a host suffering from a cellular proliferative disease by administering a combination of cisplatin active agent and a cisplatin toxicity-reducing agent.* The phrase "*suffering from a cellular proliferative disease*" **has no patentable weight** in the claim as the claim is currently drawn only to *a method of treating a host by administering a combination of cisplatin active agent and a cisplatin toxicity-reducing agent.* Prior art that reads, for example, on *a method of treating a host suffering from a fungal infection by administering a combination of cisplatin active agent and a cisplatin toxicity-reducing agent* would be 102 art since it is drawn to a method of treating a host as well. However, it would not be 102 art if current claim is written as *a method of treating a cellular proliferative disease in a host by administering a combination of cisplatin active agent and a cisplatin toxicity-reducing agent.*

Claim 17 **would be allowable if** it and the specification were rewritten or amended to overcome the rejections under 35 U.S.C. 112, 1st and 2nd paragraphs, set forth in this Office action. In the specification, the definition of the term "treatment" must be amended to remove any references to inhibit, prevent, eliminate or stopped.

If Applicant makes these amendments, the following claim drafted by the Examiner would be considered to distinguish patentably over the art of record in this application and is presented to applicant for consideration:

> Claim 17. A method of treating ovarian cancer in a patient, said method comprising: administering to said patient an amount of cisplatin effective to treating said cancer in conjunction with an amount of TK-211 effective to reducing the toxicity of said cisplatin.

If claims 18-24 were amended according to MPEP guidelines to read consistent with the limitations of Examiner-recommended claim 17, then these claims would be allowable. Claims 25-27 would have to be canceled.

Conclusion

14. The following are pertinent to this application but not relied upon for instant rejections:

a. Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE: Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep 50:219–244, 1966
b. Patricia M. Deegan, Iona S. Pratt, Michael P. Ryan, "The nephrotoxicity, cytotoxicity and renal handling of a cisplatin-methionine complex in male Wistar rats", 1994, Toxicology, 89(1), pp 1-14

c. 4,892,735 A
d. 5,059,591 A
e. 5,366,723 A
f. 5,770,576 A
g. 5,792,748 A
h. 2002/0035090 A1
i. 2004/0258771 A1

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on (571) 272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chris Simmons/CES

VICKIE KIM
PRIMARY EXAMINER